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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/967,263	09/28/2001	Timothy O'Brien	D6415	5220

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/967,263	O'BRIEN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2 and 5-18* is/are pending in the application.

4a) Of the above claim(s) *6-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed December 15, 2003 in response to the Office Action of November 5, 2003 is acknowledged and has been entered. Previously pending claims 3-4 have been canceled and claims 1-2 and 5 have been amended. Claims 1-2 and 5 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claim 1 remains rejected and newly amended claim 5 is rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Paper mailed November 5, 2003, Section 7, pages 3-12.

Applicant argues that the biological effects of one anti-HER-2/neu antibody, the humanized HERCEPTIN antibody were disclosed in the specification. It was shown that the proliferation of uterine serous papillary carcinoma cells was significantly inhibited by the HERCEPTIN antibody and the tumor cells were highly sensitive to HERCEPTIN-mediated antibody dependent cellular cytotoxicity and this example provides sufficient enablement, commensurate in scope with the claimed invention for all humanized anti-HER-2/neu antibodies.

The argument has been considered but has not been found persuasive because Applicant has not addressed the issues raised drawn to (1) the specification teaching that it is HERCEPTIN and not "any" Her-2/neu antibody that is postulated as a novel and attractive therapeutic strategy in uterine serous papillary carcinoma

patients, (2) the lack of teaching of how to make a therapeutic antibody that will function as claimed in light of the teaching of Stancovski et al, of record, Lewis et al of record, US Patent No. 5,6771,171, Strobel et al, of record, (3) the expected cross reactivity of the broadly claimed antibody, (4) the Santin et al (Clinical cancer Research, 2002, 8:1271-1279) reference wherein eight months after the filing of the instant application, the authors (also inventors of the instant application) conclude that validity of the HERCEPTIN approach to the treatment of uterine serous papillary carcinoma has not been determined. It is noted that Applicant was invited to submit objective evidence demonstrating that the invention would function as claimed with antibodies other than HERCEPTIN/Mab 4D5. Applicant has chosen not to submit the invited data.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

5. Claims 1-2 and 5 remain rejected under 35 USC 103 for the reasons previously set forth in the Paper mailed November 5, 2003, Section 10, pages 14-17.

Applicant argues that Bookman et al, (J. Clinical Oncology, 21:283-290) teaches that HERCEPETIN is not effective for treating ovarian cancer and therefore, not every HER-2/neu-overexpressing cancer is susceptible to treatment with HERCEPTIN and the effects of HERCEPTIN on a particular type of cancer cell, including uterine serous papillary carcinoma in the instant application, have to

be determined by empirical experimentation as disclosed in the present invention, thus the invention is not *prima facie* obvious and the rejection should be withdrawn.

The argument has been considered but has not been found persuasive because contrary to Applicant's argument, Bookman et al do not teach that HERCEPTIN is not effective for treating ovarian cancer. In particular, Bookman et al teach that three of the 41 patients (7.3%) achieved an objective response to HERCEPTIN (see Table 5, page 287) wherein 1 patient had a complete response for 9.7 months and two patients had partial response, one for 1.8 months and one for more than 26.9 months. Further, 16 patients (39%) met the criteria for stable disease. Further, Bookman et al state that several patients with responding or stable disease received therapy for more than 1 year, confirming the overall tolerability of the treatment regimen (p. 287, col 1). It is clear that HERCEPTIN is effective in a subset of ovarian patients whose tumor cells overexpress Her-2/neu and thus in view of the Bookman et al teaching and further for the reasons of record, it would have been *prima facie* obvious to one of ordinary skill in the art to treat any epithelial malignancy that is shown to overexpress HER-2/neu, including uterine serous papillary carcinoma, with HERCEPTIN. Given that all of Berchuck et al, Saffari et al and Wang et al specifically teach that at least a subset of patients with uterine serous papillary carcinoma overexpress HER-2/neu, one would have had a reasonable expectation of successfully treating at least a subset of said patients with HERCEPTIN.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. The specification is objected to and claim 2 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibody 4D5.

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of 4D5 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody 4D5, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when

different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, 4D5. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species, 4D5. If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

7. Claims 1 and 5 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The

limitation of a "humanized anti-HER-2/neu antibody" in the absence of the modifier "monoclonal" before "antibody" has no clear support in the specification and the claims as originally filed. A review of the specification revealed support for a HER-2/neu antibody, preferably, the antibody is a monoclonal antibody and even more preferably the antibody is a humanized monoclonal antibody on page 12, lines 5-10. A further review of the specification revealed that there was no teaching as to how to humanize an antibody that is not a monoclonal antibody. The subject matter claimed in claims 1 and 5 broadens the scope of the invention as originally disclosed in the specification. The rejection can be obviated by amending claims 1, for example to recite "a humanized anti-HER-2/neu monoclonal antibody".

8. Claims 1 and 5 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of an antibody "That binds to the p185 extracellular domain of HER-2/neu" has no clear support in the specification and the claims as originally filed. A review of the specification revealed no mention of the p185 extracellular domain and thus the specification as originally filed does not support the claimed invention. The subject matter claimed in claims 1 and 5 broadens the scope of the invention as originally disclosed in the specification.

9. No claims allowed.

10. All other objections and rejections recited in the Paper mailed December 15, 2003 are hereby withdrawn.

11. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvette Eyler, can be reached at 571-272-0871 The fax phone number for this Art Unit is (703) 305-7230.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
February 24, 2004